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11/30/98 U.S. PTO

UTILITY PATENT APPLICATION TRANSMITTAL

(Only for new nonprovisional applications under 37 CFR 1.53(b))

Attorney Docket No.	06854.0002-US01
First Named Inventor or Application Identifier	BENNEKER, et al.
Title	4-PHENYLPIPERIDINE COMPOUNDS
Express Mail Label No.	

APPLICATION ELEMENTS

See MPEP chapter 600 concerning utility patent application contents

ADDRESS TO: Assistant Commissioner for Patents
Box Patent Application
Washington, DC 20231

1. [X] *Fee Transmittal Form (Form PTO-1082)
(Submit an original and a duplicate for fee processing)

2. [X] Specification [*Total Pages* 17]
(preferred arrangement set forth below)
- Descriptive title of the Invention
- Cross References to Related Applications
- Statement Regarding Fed sponsored R&D
- Reference to Microfiche Appendix
- Background of the Invention
- Brief Summary of the Invention
- Brief Description of the Drawings (if filed)
- Detailed Description
- Claims
- Abstract of the Disclosure

3. [ ] Drawing(s) *(35 USC 113)* [*Total Sheets*]

4. Oath or Declaration [*Total Pages* 3]
a. [ ] Newly executed (original or copy)
b. [X] Copy from a prior application (37 CFR 1.63(d))
(for continuation/divisional with Box 17 completed)
[Note Box 5 below]
i. [ ] DELETION OF INVENTOR(S)
Signed statement attached deleting inventor(s) named in the prior application, see 37 CFR 1.63(d)(2) and 1.33(b).

5. [X] Incorporation By Reference *(useable if Box 4b is checked)*
The entire disclosure of the prior application, from which a copy of the oath or declaration is supplied under Box 4b, is considered as being part of the disclosure of the accompanying application and is hereby incorporated by reference therein.

6. [ ] Microfiche Computer Program *(Appendix)*

7. Nucleotide and/or Amino Acid Sequence Submission
(if applicable, all necessary)
a. [ ] Computer Readable Copy
b. [ ] Paper Copy (identical to computer copy)
c. [ ] Statement verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

8. [ ] Assignment Papers (cover sheet & document(s))
9. [X] 37 CFR 3.73(b) Statement *(when there is an assignee)* [X] Power of Attorney
10. [ ] English Translation Document *(if applicable)*
11. [X] Information Disclosure Statement (IDS)/PTO-1449 [ ] Copies of IDS Citations
12. [ ] Preliminary Amendment
13. [X] Return Receipt Postcard (MPEP 503) (Two)
(should be specifically itemized)
14. [ ] *Small Entity Statement(s) [ ] Statement filed in prior application, Status still proper and desired
15. [ ] Certified Copy of Priority Document(s)
(if foreign priority is claimed)
16. [ ] Other:

*NOTE FOR ITEMS 1 & 14: IN ORDER TO BE ENTITLED TO PAY SMALL ENTITY FEES, A SMALL ENTITY STATEMENT IS REQUIRED (37 C.F.R. § 1.27), EXCEPT IF ONE FILED IN A PRIOR APPLICATION IS RELIED UPON (37 C.F.R. § 1.28).

17. **If a CONTINUING APPLICATION,** *check appropriate box and supply the requisite information:*
[ ] Continuation [X] Divisional [ ] Continuation-in-part (CIP) of prior application No: 08/872,023
Prior Application Information: Examiner: C. Chang Group/Art Unit: 1612

18. CORRESPONDENCE ADDRESS

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Name (Print/Type)	*Mark R. Buscher*	*Registration No. (Attorney/Agent)*	35,006
Signature		*Date*	November 30, 1998

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FORM PTO-1082

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Attorney Docket No. 06854.0002-US01

ASSISTANT COMMISSIONER FOR PATENTS
Washington, D.C. 20231

Sir:

Transmitted herewith for filing is the patent application of
Inventors: BENNEKER, et al.
For: 4-PHENYLPIPERIDINE COMPOUNDS

Enclosed are:

XX 17 pages of description prior to the claims;
XX 5 pages of claims (24 claims);
XX 1 page of reference;
XX 1 page of abstract;
XX Copy of the executed inventors' Declaration from prior application no. 08/872,023;
XX Information Disclosure Statement

The filing fee has been calculated as shown below:

	(Col 1)	(Col. 2)	SMALL ENTITY			OTHER THAN A SMALL ENTITY	
FOR	NO. FILED	NO. EXTRA	RATE	FEE	OR	RATE	FEE
BASIC FEE				$ 395.00	OR		$ 760.00
TOTAL CLAIMS	24-20 =	4	x 11 =		OR	x 22 =	72.00
INDEP. CLAIMS	2-3 =	0	x 41 =		OR	x 82=	
☐ MULTIPLE DEPENDENT CLAIM PRESENTED			+ 135 =		OR	+ 260 =	260.00
*If the difference in Col. 1 is less than zero, enter "0" in Col. 2			TOTAL		OR	TOTAL	$1,092.00

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XX Any patent application processing fees under 37 CFR 1.17.

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— Any patent application processing fees under 37 CFR 1.17
— The issue fee set in 37 CFR 1.18 at or before mailing of the Notice of Allowance, pursuant to 37 CFR 1.311(b).
— Any filing fees under 37 CFR 1.16 for presentation of extra claims.

Date November 30, 1998

Mark R. Buscher (Reg. No. 35,006)

November 30, 1998

Box Patent Application

Assistant Commissioner for Patents
Washington, D.C. 20231

Re: New U.S. Non-Provisional Utility Patent Application
Appl. No. (to be assigned); Filed: (herewith)
Divisional of U.S. Appl. No. 08/872,023 , filed June 10, 1997:
For: 4-PHENYLPIPERIDINE COMPOUNDS
Inventors: FRANCISCUS BERNARDUS G. BENNEKER, FRANS VAN DALEN, JACOBUS MARIA LEMMENS, THEODORUS HENDRICUS A. PETERS, FRANTISEK PICHA
Our Ref: 06854.0002-US01

Sir:

Transmitted herewith for filing under 37 C.F.R. § 1.53(b) is a **divisional** application of prior Appl. No. 08/872,023, consisting of the following documents:

1. Utility Patent Application Transmittal Form PTO/SB/05;

2. Form PTO-1082;

3. U.S. Utility Patent Application, entitled: 4-Phenylpiperidine Compounds

and naming as inventor(s): FRANCISCUS BERNARDUS G. BENNEKER, FRANS VAN DALEN, JACOBUS MARIA LEMMENS, THEODORUS HENDRICUS A. PETERS, and FRANTISEK PICHA

the application comprising:

a. The specification containing:

(i) 17 pages of description prior to the claims;

(ii) 5 pages of claims (24 claims);

(iii) 1 page of reference;

(iv) a one (1) page abstract;

b. Copy of the executed inventors' Declaration and Power of Attorney from prior application no. 08/872,023 and copy of Revocation and Appointment of New Attorneys from prior application no. 08/872,023;

4. An Information Disclosure Statement (IDS);

5. Preliminary Amendment

Please amend the first page of the specification by inserting before the first line of text: --This application is a divisional of prior co-pending application Serial No. 08/872,023, filed June 10, 1997, the entire contents of which are incorporated herein by reference.--

6. Two (2) return post cards; and

7. Our Check No. 302110 for $1,092.00 to cover:

$ 760.00 Filing fee for patent application
$ 72.00 Fee for excess claims
$ 260.00 Multiple dependent claims.

It is respectfully requested that, of the two attached postcards, one be stamped with the filing date of these documents and returned to our courier, and the other, prepaid postcard, be stamped with the filing date and unofficial application number and returned as soon as possible.

The U.S. Patent and Trademark Office is hereby authorized to charge any fee deficiency, or credit any overpayment, to our Deposit Account No. 08-3038. A duplicate copy of this letter is enclosed.

Respectfully submitted,

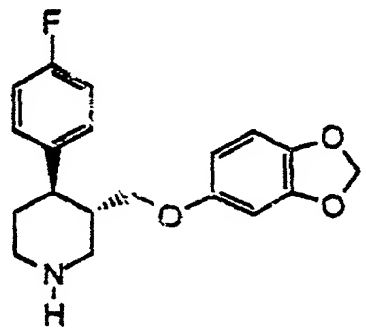
Mark R. Buscher
Reg. No. 35,006

Enclosures

4-PHENYLPIPERIDINE COMPOUNDS

The present invention relates to a group of tri-substituted, 4-phenylpiperidines, to a process for preparing such compounds, to a medicament comprising such compounds, and to the use of such compounds for the manufacture of a medicament.

The compound paroxetine, trans-4-(4'-fluorophenyl)-3-(3',4'-methylene dioxyphenoxymethyl)piperidine having the formula below:



is known and has been used in medicaments for treating, amongst other ailments, depression.

Paroxetine has been used as a therapeutic agent in the form of a salt with pharmaceutically acceptable acids. The first clinical trials were conducted with the acetate salt.

A known useful salt of paroxetine is the hydrochloride. This salt is considered to be the active substance in several marketed pharmaceutical products, e.g. Paxil or Seroxat. A number of forms of paroxetine hydrochloride have been described:

- the anhydrous form in several crystalline modifications (PCT Appl. WO 96/24595);

- the hydrated form - a hemihydrate (EP 223403) and in the solvated forms.

The comparison of behaviour between anhydrous and hydrated form of paroxetine hydrochloride is described in the Intl. Journal of Pharmaceutics, 42, 135-143 (1988).

EP 223403 discloses paroxetine hydrochloride hemihydrate and pharmaceutical compositions based thereon.

Most of these known salts of paroxetine have unsuitable physico-chemical characteristics for ensuring safe and efficient handling during production thereof and formulation into final forms, since they are unstable (acetate, maleate) and possess undesirable hygroscopicity.

Furthermore their formation by crystallization from both aqueous or non-aqueous solvents is generally low-yielded and troublesome as they usually contain an undefined and unpredicted amount of bound solvent which is difficult to remove.

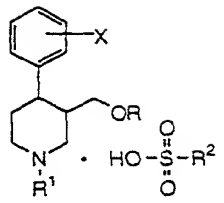
The crystalline paroxetine hydrochloride hemihydrate approaches these problems, but as stated in WO 95/16448, its limited photostability causes undesired colouration during classical wet tabletting procedure.

Moreover, crystalline paroxetine hydrochloride hemihydrate exhibits only limited solubility in water.

It has been generally suggested that where the aqueous solubility is low, for example less than 3 mg/ml, the dissolution rate at <u>in vivo</u> administration could be rate-limiting in the absorption process. The aqueous solubility of the paroxetine hemihydrate at room temperature exceeds this threshold by a relatively small margin.

An object of the present invention is to provide a compound with improved characteristics.

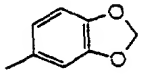
According to a first aspect, the present invention comprises a compound, and pharmaceutically acceptable salts, having the formula I:



- R represents an alkyl or alkynyl group having 1-4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,
- R^1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,
- X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy,
- R^2 represents:
  - a C1-C10 alkyl group,
  - a phenyl group optionally substituted by one or more of the following groups:
    - a C1-C10 alkyl group,
    - a halogen group,
    - a nitro group,
    - hydroxy group,
    - and/or an alkoxy group.

The inventors have found that these compounds exhibit good stability and very high solubility. This yields the advantage that high concentrations of the compound are obtainable in small volumes.

The R group is preferably the 3,4 methylenedioxyphenyl group of the formula:

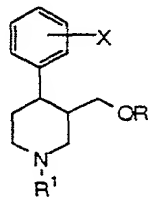


The X group is preferably a fluorine group attached to position 4 in the phenyl ring.

The R^2 group preferably represents a C1-C4 alkyl group, and most preferably represents a C1-C2 alkyl group in order to provide an optimum solubility.

The compounds can have a solubility at about 20 °C of at least about 10 mg/ml water, preferably having a solubility in water of at least 100, for example 500 and most preferably of at least 1000 mg/ml water.

According to a second aspect of the present invention, there is provided a process for preparing a compound as above, comprising the steps of mixing together a 4 phenylpiperidine compound, a salt and/or a base thereof having the formula II:



wherein:

- R represents an alkyl or alkynyl group having 1-4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino,

methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,

- R_1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,
- X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy, .

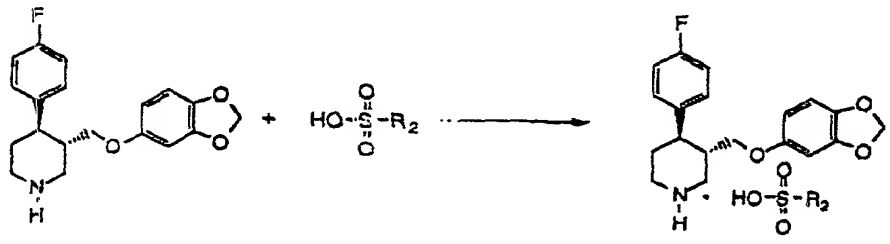
with a sulfonic acid of the general formula R_2-SO_3H, wherein R_2 represents:

- a C1-C10 alkyl group,
- a phenyl group optionally substituted by one or more of the following groups:
  - a C1-C10 alkyl group,
  - a halogen group,
  - a nitro group,
  - a hydroxy group, and/or
  - an alkoxy group,

to form a solution, followed by separating the compound formed from this solution.

The compounds of the invention can be prepared from the free base of the 4 phenylpiperidine, having the formula II, this preferably being paroxetine, by treatment with a sulfonic acid as defined above in a suitable solvent to form a solution of the desired acid addition salt, whereafter this is precipitated out of the solution.

The equation for paroxetine free base and sulfonic acids is as follows:

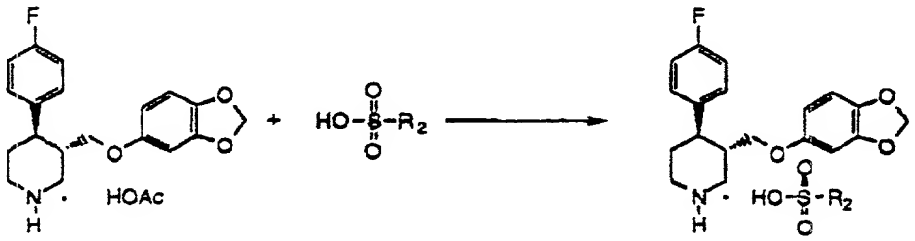


The forming of a solution may preferably proceed at temperatures from about 0 °C to the boiling point of the solvent.

Optionally, the solution may be purified by treatment of activated charcoal, silica gel, kieselguhr or other suitable materials.

Alternatively, the solution of a salt of the invention can be formed by dissolution of a salt of 4 phenyl piperidine having the formula II with an organic sulfonic acid.

For example the compounds of the invention may be prepared from a paroxetine C1-C5 carboxylate, such as the acetate, by addition of corresponding organic sulfonic acid to the solution of the said carboxylate, as follows:

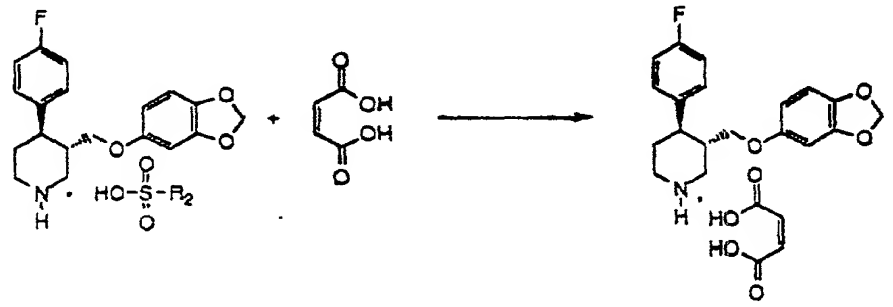


According to a third aspect of the present invention, there is provided a compound obtainable by this process.

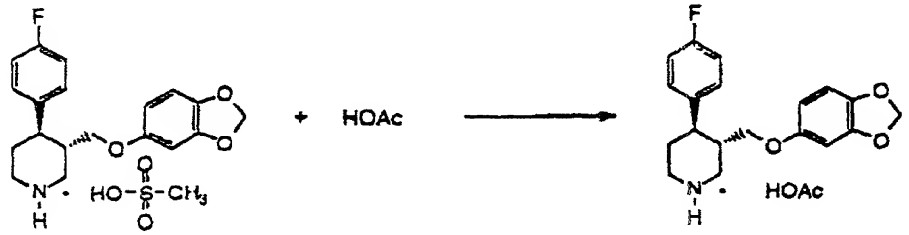
According to a fourth aspect of the present invention there is provided the above compound for use as a medicament and, according to a fifth aspect, a medicament comprising this compound, and to the use thereof for treating depressions, obsessive compulsive disorders, panic disorders, bulimia, anorexia, pain, obesity, senile demential, migraine, anorexia, social phobia, depressions arising from pre-menstrual tension.

According to a sixth aspect of the present invention, there is provided the use of a compound of the

invention as a reagent in further syntheses. More specifically, the compounds of the present invention can be used as a start reagent for forming further acid addition salts, for example for providing further paroxetine acid addition salts, by reacting with a suitable reagent, i.e. with a corresponding acid. For example, the formation of paroxetine maleate according to the present invention proceeds by the following equation:



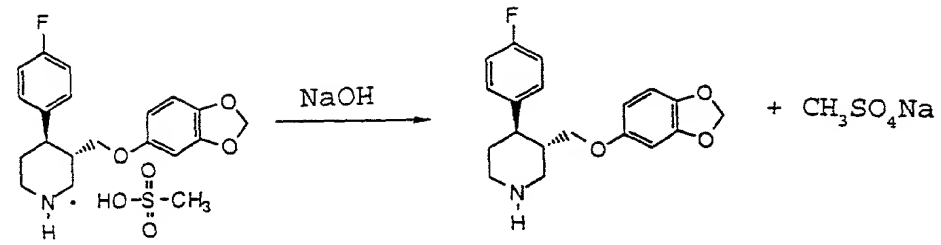
and the formation of paroxetine acetate proceeds as follows:



This is an advantageous route, since by using the substantially pure sulfonic acid salts according to the present invention as a start reagent, the preparation of a further salt, as above, results in this further salt having a high purity. The inventors have shown that such salts have a surprisingly high purity.

Similarly, the compounds of the present invention can react with a base, such as an inorganic and/or an organic base, to form (liberate) free bases of the corresponding compounds. As exemplified on

paroxetine, the reaction proceeds according to the equation:



The free bases liberated from the compounds of the present invention have surprisingly higher purity than if prepared by known methods which is especially important in case of their use for production of pharmaceuticals.

Accordingly, the new compounds of the first aspect of the invention can also form hydrates and/or solvates by a contact with a corresponding reaction partner, i.e. with water and/or with a solvent. Examples of such further salts, hydrates and solvates, for example these of paroxetine, are the:

hydrochloride	oxalate	dihydrate
hydrobromide	succinate	trihydrate
hydroiodide	tartrate	hexahydrate
acetate	citrate	methanolate
propionate	embonate	ethanolate
maleate	hemihydrate	
fumarate	hydrate	

The inventors have shown that such salts have a surprisingly high purity.

Examples of bases which can be employed in the preparation of the free bases are: sodium hydroxide, potassium hydroxide, calcium hydroxide, ammonium hydroxide, sodium carbonate, methylamine, dimethylamine, triethylamine, pyridine and such like.

Since the compounds according to the present invention exhibit high solubility, they can be dosed, for

example injected, in a high concentration, low volume solution, this method of dosing being particularly advantageous with certain patients, such as manic depressives and such like, i.e. patients who are unable or unwilling to swallow medicine.

The compounds of the present invention can be formulated into various types of pharmaceutical compositions for treatment of humans and animals. Pharmaceutical compositions according to the present invention comprise a compound of the invention alone or together with a pharmaceutically acceptable carrier or diluent. The preferred formulations are those for oral administration (tablets, capsules) but formulations for parenteral or topical administration are also within the scope of the invention. The high water solubility of the compounds of the invention enables high dissolution rates in solid dosage forms based on the compounds of the invention to be obtained, during the <u>in vitro</u> release as well as good bioavailability after peroral application <u>in vivo</u>.

The tablets containing compounds of the present invention can be prepared both by tabletting procedure in which water is present (e.g. aqueous granulation) as well as by tabletting processing it which water is absent (direct compression, dry granulation) and may be coated by any suitable means of coating.

The present invention will now be further elucidated by way of the following examples and results.

EXPERIMENTAL

A seeding crystal of paroxetine methane sulfonate was made as follows:
2.7 g (8.2 mmol) of paroxetine was dissolved in 15 ml of hot ethanol.
1.0 g (10.4 mmol) of methanesulfonic acid in 15 ml of ethanol was added and the mixture was cooled to room temperature. When the mixture had

reached room temperature the mixture was put in the freezer at -20 °C overnight. No crystal line compound was obtained.
The mixture was evaporated to dryness leaving an oil.
After 1 month at room temperature a waxy solid was obtained. Part of this solid was taken apart and the rest was dissolved in
10 ml of EtOAc. The waxy crystals were added and the mixture was put in the freezer at -20 °C overnight. A white crystalline product was precipitated. After filtration and drying in a vacuumoven
2.5 g (5.9 mmol) of paroxetine methane sulfonate was obtained.
Yield 72%
This seeding crystal was subsequently used in following examples 1 and 3.

Examples

Example 1

Paroxetine methane sulfonate from paroxetine

To a solution of 43.5 g (132 mmol) of paroxetine, prepared by the procedure disclosed in US 4007196,
12.7 g (132 mmol) of methane sulfonic acid was added to
150 ml of boiling ethyl acetate. The mixture was left at room temperature for 2 hours. Subsequently the mixture was placed overnight at -20 °C, with a seeding crystal. The obtained solid was filtered off and washed with
50 ml of ether. The obtained white solid was dried overnight in a vacuumoven.
47.1 g (111 mmol) of product
Yield 99.5%

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 98% (HPLC).

Example 2

Paroxetine benzene sulfonate from paroxetine

3.8 g (11.5 mmol) of paroxetine was dissolved in 10 ml of hot ethylacetate.

1.82 g (11.5 mmol) of anhydrous benzenesulfonic acid was added. The mixture was left at room temperature for 2 h. The mixture was evaporated to dryness and dissolved in dichloromethane, and evaporated again to dryness leaving an oil. This oil was solidified through high vacuum (0.1 mmHg) evaporation leaving

5.0 g (1.3 mmol) of an off white solid. To this solid was added

5 ml of acetone and the suspension was stirred for 5 minutes during which a white suspension was obtained. The solid was filtered off and dried under vacuum.

4.8 g (9.9 mmol) of product was obtained.

Yield 85%

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC).

Example 3

Paroxetine p-toluene sulfonate from paroxetine

5.0 g (15 mmol) of paroxetine was dissolved in 25 ml of hot ethylacetate.

2.9 g (15 mmol) of p-toluenesulfonic acid was added. The mixture was left at room temperature for 2 h and subsequently put in the freezer, with a seeding crystal, for 14 h. The solid was filtered off and washed once with

10 ml of n-hexane. The obtained white solid was dried overnight in a vacuumoven.

4.8 g (10 mmol) of a white solid was obtained. Yield 67%

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC).

Example 4

Paroxetine p-chlorobenzene sulfonate from paroxetine

1.1 g (3.3 mmol) of paroxetine was dissolved in 3 ml of hot ethylacetate.

0.76 g (3.3 mmol) of 90% p-chlorobenzenesulfonic acid was added. The mixture was left at room temperature for 1 h and washed with 5 ml of water. The organic layer was dried with Na_2SO_4, filtered and evaporated to dryness leaving

1.5 g (2.9 mmol) of an off white solid. Yield 88%

Analytical characterization of the compound obtained is shown in Table 1. The purity of the compound obtained was 99.4% (HPLC).

Example 5

Paroxetine maleate from paroxetine methane sulfonate

1.0 g (2.4 mmol) of paroxetine methane sulfonate in 5 ml of hot water. To this solution was added

0.32 g (2.8 mmol) of maleic acid. The mixture was placed at 4 °C overnight after which a solid with a yellow oil was precipitated on the bottom of the flask. The solid/oil was filtered off and washed 3 times with 10 ml of ether and dried in a vacuumoven.

0.8 g (2.0 mmol) off white crystals were obtained Yield 85%

The purity of the compound obtained was 99.5% (HPLC).

Example 6

Paroxetine acetate from paroxetine methane sulfonate

1.0 g (2.4 mmol) of paroxetine methane sulfonate in 5 ml of hot iso-propanol. To this solution was added 0.2 g (3.2 mmol) of acetic acid. The mixture was placed at 4 °C overnight after which a solid was precipitated. The solid was filtered off and washed 3 times with 10 ml of ether and dried in a vacuumoven. 0.5 g (1.3 mmol) off white crystals were obtained
Yield 54%
The purity of the compound obtained was 99.5% (HPLC).

Example 7

Paroxetine free base from paroxetine methane sulfonate

10.0 g (24.0 mmol) of paroxetine methane sulfonate in 150 ml of water and 200 ml of ethyl acetate. To this was added 12.4 g (31 mmol) of an aqueous 10 wt% NaOH solution and the suspension was stirred for 15 minutes. The layers were separated and the aqueous layer was extracted once with 50 ml of ethyl acetate. The combined organic layers are washed once with 100 ml of water and dried over Na_2SO_4. The Na_2SO_4 was filtered off and washed once with 50 ml of ethyl acetate. The ethyl acetate was evaporated off, leaving 7.5 g (22.8 mmol) of an oily product.
Yield 95%
The purity of the compound obtained was 99.5% (HPLC).

A number of the compounds obtained were analysed, the results being shown in tables 1-5 below:

Table 1 Characterization of salts of paroxetine with certain organic sulfonic acids R-SO_3H
R = CH_3 - (paroxetine methane sulfonate): m.p.: 142°-144°C. DSC curve (closed pan, 10°C/min): onset 145.8°C, 79.0 J/g. IR spectrum (KBr, in cm^{-1}): 531, 546, 777, 838, 931, 962, 1038, 1100, 1169, 1208, 1469, 1500, 1515, 1615, 2577, 2869, 2900, 3023. 1H-NMR (ppm): 1.99 (br d, H_{5eq}, 1H); 2.27 (ddd, H_{5ax}, 1H); 2.48-2.65 (m, H_3, 1H); 2.82-2.92 (m, H_4 , CH_3, 4H); 2.95-3.20 (m, H_{2ax}, H_{6ax}, 2H); 3.47 (dd , H_7, 1H); 3.58-3.74 (m, H_{2eq}, H_{6eq}, H_7, 3H); 5.88 (s, $H_{7''}$, 2H); 6.10 (dd, $H_{6''}$, 1H); 6.33 (d, $H_{2''}$, 1H); 6.61 (d, $H_{5''}$, 1H); 7.09 (dd, $H_{3'}$, $H_{5'}$, 2H); 7.22 (dd , $H_{2'}$, $H_{6'}$, 2H); 8.85 (br d, NH_{eq}, 1H); 9.11 (br d, NH_{ax}, 1H). 13C-NMR (ppm): 30.0 (s, C_5); 39.3 (s, C_3); 39.5 (s, C_4); 41.7 (s, SC); 44.6 (s, C_6); 46.8 (s, C_2); 67.4 (s, C_7); 97.8 (s, $C_{2''}$); 101.2 (s, $C_{7''}$); 105.4 (s, $C_{6''}$); 107.8 (s, $C_{5''}$); 115.8 (d, $C_{3'}$, $C_{5'}$); 128.4 (s, $C_{6'}$, $C_{2'}$); 137.1 (s, $C_{4''}$); 142.0 (s, $C_{1'}$); 148.2 (s, $C_{3''}$); 153.7 (s, $C_{1''}$); 161.9 (d, $C_{4'}$).
R = *C_6H_5- (paroxetine benzene sulfonate)*: m.p.: 55°-60°C. IR spectrum (KBr, in cm^{-1}): 530, 564, 614, 689, 728, 764, 828, 929, 993, 1007, 1029, 1121, 1179, 1229, 1443, 1471, 1486, 1514, 1600, 1628, 2557, 2842, 3029. 1H-NMR (ppm): 1.90 (br d, H_{5eq}, 1H); 2.10-2.28 (m , H_{5ax}, 1H); 2.38-2.52 (m, H_3, 1H); 2.82 (ddd, H_4, 1H); 3.02-3.18 (m, H_{2ax}, H_{6ax}, 2H); 3.37 (dd, H_7, 1H); 3.48 (d, H_7, 1H); 3.60-3.82 (m, H_{2eq}, H_{6eq}, 2H); 5.87 (s, $H_{7''}$, 2H); 6.06 (dd, $H_{6''}$, 1H); 6.29 (d, $H_{2''}$, 1H); 6.60 (d, $H_{5''}$, 1H); 6.90 (dd, $H_{3'}$, $H_{5'}$, 2H); 7.04 (dd, $H_{2'}$, $H_{6'}$, 2H); 7.40 (d, *ArH*, 3H); 7.94 (d, *SArH*, 2H); 8.81 (br d, NH_{eq}, 1H); 9.04 (br d, NH_{ax} 1H). 13C-NMR (ppm): 29.9 (s, C_5); 39.2 (s, C_3); 41.5 (s, C_4); 44.8 (s, C_6); 47.0 (s, C_2); 67.3 (s, C_7); 97.9 (s, $C_{2''}$); 101.2 (s, $C_{7''}$); 105.5 (s, $C_{6''}$) 107.8 (s, $C_{5''}$); 115.7 (d, $C_{3'}$, $C_{5'}$); 125.9 (s, C_b); 128.6 (s, C_d); 128.8 (s, $C_{6'}$, $C_{2'}$); 130.6 (s, $C_{c\pi}$); 137.1 (s, $C_{4''}$); 141.9 (s, $C_{1'}$); 144.1 (s, C_a); 148.2 (s, $C_{3''}$); 153.7 (s, $C_{1''}$); 161.8 (s, $C_{4'}$).
R = *$p\text{-}CH_3C_6H_4$ (paroxetine p-toluene sulfonate)*: m.p.: 148°-150°C. DSC curve (closed pan, 10°C/min): onset 151.6°C, 71.6 J/g. IR spectrum (KBr, in cm^{-1}): 529, 557, 671, 771, 800, 814, 921, 936, 1000, 1029, 1100, 1157, 1186, 1229, 1471, 1486, 1507, 1600, 2557, 2829, 3029. 1H-NMR (ppm): 1.89 (br d, H_{5eq}, 1H); 2.10-2.50 (m, H_{5ax}, H_3, CH_3, 5H); 2.82 (ddd, H_4, 1H); 2.97-3.18 (m, H_{2ax}, H_{6ax}, 2H); 3.36 (dd, H_7, 1H); 3.48 (dd, H_7, 1H); 3.52-3.77 (m, H_{2eq}, H_{6eq}, 2H); 5.87 (s, $H_{7''}$, 2H); 6.06 (dd, $H_{6''}$,1H); 6.28

Table 1 (continued) Characterization of salts of paroxetine with certain organic sulfonic acids R-SO_3H
(d, $H_{2''}$, 1H); 6.59 (d, $H_{5''}$, 1H); 6.90 (dd, $H_{3'}$, $H_{5'}$, 2H); 7.05 (dd, $H_{2'}$, $H_{6'}$, 2H); 7.24 (d, CH_3ArH, 2H); 7.83 (d, $SArH$, 2H); 8.91 (br d, NH_{eq}, 1H); 9.17 (br d, NH_{ax}, 1H). 13C-NMR (ppm): 21.3 (s, C_e); 29.9 (s, C_5); 39.2 (s, C_3); 41.5 (s, C_4); 44.7 (s, C_6); 46.9 (s, C_2); 67.3 (s, C_7); 97.8 (s, $C_{2''}$); 101.1 (s, $C_{7''}$); 105.5 (s, $C_{6''}$); 107.8 (s, $C_{5''}$); 115.6 (d, $C_{3'}$, $C_{5'}$); 125.8 (s, C_b); 129.0 (s, $C_{6'}$, $C_{2'}$); 129.1 (s, C_c); 137.2 (s, $C_{4''}$); 140.8 (s, C_d); 141.5 (s, C_a); 141.9 (s, $C_{1'}$); 148.2 (s, $C_{3''}$); 153.8 (s, $C_{1''}$); 161.8 (d, $C_{4'}$).
R = *p-ClC_6H_4 (paroxetine p-chlorobenzene sulfonate)*; m.p.: 75°-80°C. IR spectrum (KBr, in cm^{-1}): 486, 557, 643, 736, 821, 1000, 1029, 1086, 1114, 1186,1229, 1471, 1486, 1514, 1600, 1657, 2857, 3029. 1H-NMR (ppm): 1.91 (br d, H_{5eq}, 1H); 2.15 (ddd, H_{5ax}, 1H); 2.37-2.52 (m, H_3, 1H); 2.81 (ddd, H_4, 1H); 2.93-3.21 (m, H_{2ax}, H_{6ax}, 2H); 3.37 (dd, H_7, 1H); 3.49 (d, H_7, 1H); 3.61-3.81 (m, H_{2eq}, H_{6eq}, 2H); 5.88 (s, $H_{7''}$, 2H); 6.05 (dd, $H_{6''}$, 1H); 6.27 (d, $H_{2''}$, 1H); 6.59 (d, $H_{5''}$, 1H); 6.91 (dd, $H_{3'}$, $H_{5'}$, 2H); 7.03 (dd, $H_{2'}$, $H_{6'}$, 2H); 7.39 (d, $ClArH$, 2H); 7.86 (d, $SArH$, 2H); 8.78 (br d, NH_{eq}, 1H); 9.02 (br d, NH_{ax}, 1H). 13C-NMR (ppm): 30.0 (s, C_5); 39.3 (s, C_3); 41.5 (s, C_4); 44.9 (s, C_6); 47.1 (s, C_2); 67.3 (s, C_7); 97.9 (s, $C_{2''}$); 101.2 (s, $C_{7''}$); 105.5 (s, $C_{6''}$); 107.9 (s, $C_{5''}$); 115.8 (d, $C_{3'}$, $C_{5'}$); 127.6 (s, C_b); 128.8 (s, $C_{6'}$, $C_{2'}$); 132.0 (s, C_d); 137.0 (s, C_c); 137.2 (s, $C_{4''}$); 141.8 (s, $C_{1'}$); 142.0 (s, C_a); 148.2 (s, $C_{3''}$); 153.6 (s, $C_{1''}$); 161.8 (d, $C_{4'}$).

The compounds of the invention are crystalline, with defined melting points, DSC curves and IR spectra. It cannot be excluded that, under different conditions of their formation and under specific conditions, they could exist also in other crystalline or polymorph modifications which may differ from those as described herein. The compounds of the invention are also generally very stable and non-hygroscopic.

It should be understood that the present invention comprising acid addition salts with organic sulfonic acids are substantially free of the bound organic solvent. Preferably, the amount of bound organic solvent should be less than 2.0% (w/w) as calculated on the anhydrous basis. They nevertheless may contain crystallization water and also unbound water, that is to say water which is other than water of crystallization.

In the following tables 2 and 3, examples of results of hygroscopicity tests and stability tests (in comparison with known salts of paroxetine) are presented.

Table 2
Hygroscopicity of certain salts of paroxetine (40°C, 75 % rel.hum).

water content (in %) at	t = 0	t = 4 weeks
methane sulfonate	0.35	+ 0.04
p-toluene sulfonate	0.70	< 0.02
hydrochloride	-	+ 2.5

Table 3
Solubility of paroxetine salts in water (in mg/ml)

	20°C	50°C
methane sulfonate	> 1000 / 10 min	1300
p-toluene sulfonate	> 1000	> 1000
hydrochloride hemihydrate	4.9	12.6
hydrochloride anhydrate	8.2	24.2

Table 4
Stability of paroxetine salts by HPLC (total amount of degradation in %).

	degradation 20°C	80°C
methane sulfonate	not observed	< 0.2 %, 3 months
p-toluene sulfonate	not observed	< 0.2 %, 3 months
maleate	0.2 %, 12 months	> 50 %, 5 days

Table 5
Solubility of salts of paroxetine in nonaqueous solvents (in mg/ml)

		methane sulfonate	p-toluene sulfonate
Ethanol	20°C	36	50
	78°C	250	> 500
2-Propanol	20°C	7	14
	82°C	330	> 500
Acetone	20°C	5	16
	56°C	37	125
Ethyl acetate	20°C	2	22
	77°C	25	> 500
n-Hexane	20°C	< 0.05	< 0.05
	69°C	0.05	< 0.05

Examples of analytical data of the paroxetine salts and the free base prepared in Examples 5 to 7 are given in Table 6.

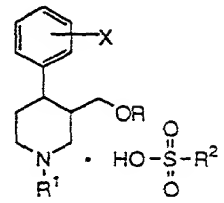
Table 6
Characterization of salts / free base of paroxetine

paroxetine maleate: m.p.: 128-130°C. 1H-NMR (ppm): 1.65-2.00 (m, H_{5eq}, H_{5ax}, 2H); 2.00-2.50 (m, H_3, 1H); 2.55-3.15 (m, H_{2ax}, H_{6ax}, H_4, 3H); 3.15-3.75 (m, H_{2eq}, H_{6eq}, H_7, 3H); 5.67 (s, $H_{7''}$, 2H); 5.97 (s, H_a, 1H); 6.12 (dd, $H_{6''}$, 1H); 6.42 (d, $H_{2''}$, 1H); 6.67 (d, $H_{5''}$, 1H); 6.95-7.35 (m, $H_{2'}$, $H_{3'}$, $H_{5'}$, $H_{6'}$, 4H).
paroxetine acetate: m.p.: 123-125°C. 1H-NMR (ppm): 1.70-2.00 (m, H_{5eq}, H_{5ax}, 2H); 1.97 (s, H_a, 3H); 2.05-2.50 (m, H_3, 1H); 2.50-3.00 (m, H_4, H_{2ax}, H_{6ax}, 3H); 3.05-3.75 (m, H_{2eq}, H_{6eq}, H_7, 3H); 6.05 (s, $H_{7''}$, 2H); 6.28 (dd, $H_{6''}$, 1H); 6.58 (d, $H_{2''}$, 1H); 6.65 (d, $H_{5''}$, 1H); 7.10-7.50 (m, $H_{2'}$, $H_{3'}$, $H_{5'}$, $H_{6'}$, 4H).
paroxetine: 1H-NMR (ppm): 1.60-2.00 (m, H_{5ax}, H_{5eq}, 2H); 2.00-2.35 (m, H_3, 1H); 2.40-2.95 (m, H_4, H_{2ax}, H_{6ax}, 3H); 3.15-3.70 (m, H_{2eq}, H_{6eq}, H_7, 2H); 5.67 (s, $H_{7''}$, 2H); 6.11 (dd, $H_{6''}$,1H); 6.43 (d, $H_{2''}$, 1H); 6.62 (d, $H_{5''}$, 1H); 6.80-7.35 (m, $H_{2'}$, $H_{3'}$, $H_{5'}$, $H_{6'}$, 4H).

It will be clear that the invention is not limited to the above description, but is rather determined by the following claims.

CLAIMS

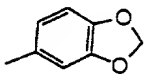
1. A compound, and pharmaceutically acceptable salts, having the formula I:



wherein:

- R represents an alkyl or alkynyl group having 1-4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,
- R^1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,
- X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy,
- R^2 represents:
  - a C1-C10 alkyl group,
  - a phenyl group optionally substituted by one or more of the following groups:
    - a C1-C10 alkyl group,
    - a halogen group,
    - a nitro group,
    - hydroxy group,
    - and/or an alkoxy group.

2. Compound according to claim 1, wherein the R group is the 3,4 methylene dioxy phenyl group of the formula:



3. Compound according to claim 1 or 2, wherein the X group is preferably a fluorine group attached to position 4 in the phenyl ring.

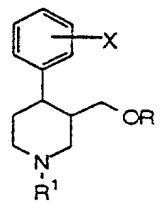
4. Compound according to claim 1-3, wherein the R^2 group represents a C1-C4 alkyl group.

5. Compound according to claims 1-4, wherein the R^2 group is a C1-C2 alkyl group.

6. Compound according to any of the previous claims, having a solubility at about 20 °C of at least about 10 mg per ml water.

7. Compound according to claim 6, having a solubility in water of at least 100, preferably at least 500 and most preferably of at least 1000 mg per ml.

8. Process for preparing a compound according to any of the previous claims, comprising the steps of mixing together a compound, a salt and/or a base thereof, having the formula II:



wherein:

- R represents an alkyl or alkynyl group having 1-4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,
- R^1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,
- X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy, with a sulfonic acid of the general formula R^2-SO_3H, wherein R^2 represents:
  - a C1-C10 alkyl group,
  - a phenyl group optionally substituted by one or more of the following groups:
    - a C1-C10 alkyl group,
    - a halogen group,
    - a nitro group,
    - hydroxy group,
    - and/or an alkoxy group,

to form a solution, whereafter the solid formed may be separated out.

9. Compound according to any of the claims 1-7 obtainable by the process according to claim 8.

10. Compound according to any of the claims 1-7 and 9, for use as a medicament.

11. Medicament comprising a compound according to any of the claims 1-7, 9, 10 and pharmaceutically acceptable carriers/diluents.

12. Use of a compound according to any of the claims 1-7, 9, 10 for preparing a medicament.

13. Use of a compound according to any of the claims 1-7 for the manufacture of a medicament for treating depressions, obsessive compulsive disorders, panic disorders, bulimia, anorexia, pain, obesity, senile demential, migraine, anorexia, social phobia, depressions arising from pre-menstrual tension.

14. Use of a compound according to any of the claims 1-7, 9, 10 as a reagent in further syntheses.

15. Process for providing a salt ion or solvate, comprising the steps of mixing together a compound according to any of the claims 1-7, 9 and 10 with a reagent selected from the group consisting essentially of:

hydrochloric acid	citric acid
hydrobromic acid	embonic acid/pamoic acid
hydriodic acid	sulfuric acid
acetic acid	water
propionic acid	methanol
maleic acid	ethanol
fumaric acid	
oxalic acid	
succinic acid	
tartaric acid	

16. Salt obtainable by the process according to claim 15.

17. Salt according to claim 16, having a purity of at least 90 wt%, preferably at least 95 wt% and most preferably at least 98%.

18. Paroxetine maleate having a purity of at least 98%.

19. Paroxetine acetate having a purity of at least 98%.

20. Process for providing a free base comprising the step of mixing together a compound according to any of the claims 1-7, 9, 10 with an organic and/or inorganic base.

21. Process according to claim 20, wherein the base is selected from the group consisting essentially of: sodium hydroxide, potassium hydroxide, calcium hydroxide, ammonium hydroxide, sodium carbonate, methylamine, dimethylamine, triethylamine, pyridine.

22. A free base obtainable by the process according to claims 20 or 21, said free base having a purity of at least 95% and most preferably at least 98%.

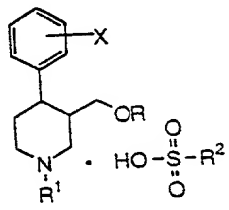
23. Paroxetine free base according to claim 22, having a purity of at least 98%.

Reference

- Psychopharmacology, 57, 151-153 (1978)]; ibid. 68, 229-233 (1980), European Journal of Pharmacology, 47, 351-358 (1978)]; in USP 4007196, the preparation of paroxetine maleate is reported.

ABSTRACT

The invention relates to a compound, and pharmaceutically acceptable salts, having the formula I:



wherein:

- R represents an alkyl or alkynyl group having 1-4 carbon atoms, or a phenyl group optionally substituted by C_{1-4} alkyl, alkylthio, alkoxy, halogen, nitro, acylamino, methylsulfonyl or methylenedioxy, or represents tetrahydronaphthyl,
- R^1 represents hydrogen, trifluoro (C_{1-4}) alkyl, alkyl or alkynyl,
- X represents hydrogen, alkyl having 1-4 carbon atoms, alkoxy, trifluoroalkyl, hydroxy, halogen, methylthio or aralkoxy,
- R^2 represents:
  - a C1-C10 alkyl group,
  - a phenyl group optionally substituted by one or more of the following groups:
    - a C1-C10 alkyl group,
    - a halogen group,
    - a nitro group,
    - hydroxy group,
    - and/or an alkoxy group.

Declaration and Power of Attorney For Patent Application

English Language Declaration

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

4-PHENYLPIPERIDINE COMPOUNDS

the specification of which

(check one)

☐ is attached hereto.

☒ was filed on 10 June 1997 as

Application Serial No. 08/872,023

and was amended on _____ (if applicable)

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, §1.56(a).

I hereby claim foreign priority benefits under Title 35, United States Code, §119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)			Priority Claimed	
(Number)	(Country)	(Day/Month/Year Filed)	☐ Yes	☐ No
(Number)	(Country)	(Day/Month/Year Filed)	☐ Yes	☐ No
(Number)	(Country)	(Day/Month/Year Filed)	☐ Yes	☐ No

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, §1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)
(Application Serial No.)	(Filing Date)	(Status) (patented, pending, abandoned)

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Franciscus B.G. Benneker, et al. Appl. No. 08/872,023 Filed: June 10, 1997 For: 4-Phenylpiperidine Compounds	Atty. Docket: 06854.0002

Revocation of Prior Power of Attorney and Appointment of New Attorneys of Record

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Synthon B.V. is the assignee of the entire right, title and interest in the above-captioned application by virtue of the assignment recorded at the U.S. Patent and Trademark Office on December 16, 1997 at reel 8866, frame 0085. The undersigned, having express authority to represent Synthon B.V., hereby revokes all powers of attorney heretofore given in the above-captioned application and appoints as his attorneys Jeffrey I. Auerbach, Reg. No. 32,680; Melvin L. Barnes, Jr., Reg. No. 38,375; Michael J. Bell, Reg. No. 39,604; Mark R. Buscher, Reg. No. 35,006; Celine T. Callahan, Reg. No. 34,301; Cono A. Carrano, Reg. No. 39,623; James F. Davis, Reg. No. 21,072; Thomas M. Dunham, Reg. No. 39,965; Joel M. Freed, Reg. No. 25,101; Alan M. Grimaldi, Reg. No. 26,599; Alexander J. Hadjis, Reg. No. 36,540; Albert P. Halluin, Reg. No. 25,227; Michael N. Haynes, Reg. No. 40,014; Richard H. Kjeldgaard, Reg. No. 30,186; Joseph P. Lavelle, Reg. No. 31,036; David R. Marsh, Reg. No. 41,408; Kevin W. McCabe, Reg. No. 41,182; Joseph A. Micallef, Reg. No. 39,772; Anthony D. Miller, Reg. No. 34,394; Karen L. Nicastro, Reg. No. 35,968; Stephen J. Pentlicki, Reg. No. 40,125, Andrea G. Reister, Reg. No. 36,253; Stephen J. Rosenman, Reg.

No. 29,209; Timothy L. Scott, Reg. No. 37,931; Anthony W. Shaw, Reg. No. 30,104; J. David Smith, Reg. No. 39,839; and Michael J. Songer, Reg. No. 39,841, with full power of substitution, association, and revocation, to prosecute said application and to transact all business in the United States Patent and Trademark Office connected therewith.

The undersigned hereby grants said attorneys the power to insert on this Power of Attorney any further identification that may be necessary or desirable in order to comply with the rules of the U.S. Patent and Trademark Office.

Kindly address all further communications relating to this application to the following:

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Box No. 34
1299 Pennsylvania Avenue, N.W.
Washington, DC 20004-2402

Direct Phone Calls to Mark R. Buscher, Esq. at (202) 383-6986.

On behalf of Synthon B.V.:

FOR: Synthon B.V.

SIGNATURE: _____

BY: Jacques M. Lemmens

TITLE: President

DATE: 10-03-1998

Certificate Under 37 C.F.R. § 3.73(b)

Applicant(s): Franciscus B.G. Benneker, et al.

Application No: 08/872,023 Filed: June 10, 1997

For: 4-Phenylpiperidine Compounds

Synthon B.V., a Corporation
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is the assignee of the entire right, title and interest in the patent application identified above by virtue of either:

A. [X] An Assignment from the inventor(s) of the patent application identified above. The assignment was recorded in the Patent and Trademark Office at Reel 8866, Frame 0085, or for which a copy thereof is attached.

[or]

B. [ ] A chain of title from the inventor(s) of the patent application identified above to the current assignee as shown below:

1. From: _____ To: _____
The document was recorded in the Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

2. From: _____ To: _____
The document was recorded in the Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

3. From: _____ To: _____
The document was recorded in the Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.

[ ] Additional documents in the chain of title are listed on a supplemental sheet.

[ ] Copies of assignments or other documents in the chain of title are attached.

To the best of the undersigned's knowledge and belief, title of the patent application identified above is in the assignee identified above.

The undersigned (whose title is supplied below) is empowered to act on behalf of the assignee.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further, that these statements are made with the knowledge that willful false statements, and the like so made, are punishable by fine or imprisonment, or both under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 10-03-1998

Name: Jacques M. Lemmens

Title: President

Signature: _____